PATENT
P-4423D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S): D. J. Wright et al.

SERIAL. NO.: 09/778,168 ART UNIT: 1655

FILING DATE: February 7, 2001 EXAMINER: B. Forman

FOR: METHODS AND OLIGONUCLEOTIDES FOR DETECTING NUCLEIC ACID SEQUENCE VARIATIONS

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231

ON: DECEMBER 5, 2001
(DATE OF DEPOSIT)

BY: URSULA M POLIGNONE
(NAME)

Ursula M Polignone 12/5/01
(SIGNATURE) (DATE)

AMENDMENT PURSUANT TO 37 C.F.R. §1.111

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed on July 5, 2001 (Paper No.3), please amend the present application as follows and consider the remarks set forth below.

IN THE CLAIMS:

Please cancel claim 2 without prejudice.

Please amend the claims as follows.

1.(amended) A method for identifying a single nucleotide polymorphism in a target in an isothermal nucleic acid amplification reaction, said method comprising:

a) hybridizing a detector primer to the target, wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism located about one to four nucleotides 5′ of a 3′ terminal nucleotide of the detector primer which is complementary to the target sequence;

b) amplifying the target by hybridization and extension of the detector primer;

c) determining whether the efficiency of said detector primer extension is greater, lesser or equal to the efficiency of extension of a detector primer without said diagnostic nucleotide; and

d) detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of detector primer extension.

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a2

3.(amended) The method of Claim 1 wherein the single nucleotide polymorphism is identified using two or more detector primers, each comprising a different diagnostic nucleotide.

4.(amended) The method of Claim 3 wherein two detector primers are used to identify which of two possible single nucleotide polymorphisms is present in the target sequence.

5.(amended) The method of Claim 3 wherein four detector primers are used to identify the single nucleotide polymorphism.

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a3

13.(amended) The method of Claim 1 wherein the isothermal amplification reaction is selected from the group consisting of Strand Displacement Amplification (SDA), Self-Sustaining Sequence Replication (3SR), Nucleic Acid Sequence Based Amplification (NASBA), and Transcription Mediated Amplification (TMA).

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a4

17.(amended) The method of Claim 1 wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label attached to the detector primer.

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a5

19.(amended) The method of Claim 18 wherein the label is a fluorescent donor/quencher dye pair and a decrease in donor dye fluorescence is detected as identifying the presence of the single nucleotide polymorphism.

20.(amended) The method of Claim 19 wherein a change in fluorescence polarization is detected as identifying of the presence of the single nucleotide polymorphism.

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a6

22.(amended) The method of Claim 1 further comprising, prior to amplifying, displacing the hybridized detector primer from the target by extension of an upstream primer, and hybridizing the detection primer to the target.

REMARKS

Paper No. 3 presented rejections of the claims as: (1) indefinite under 35 U.S.C. §112, second paragraph; and (2) obvious under 35 U.S.C. §103 (a). Each of theses issues is addressed below.

I. Indefiniteness

A. Claims 1-22 were rejected as indefinite for the recitation "in an isothermal nucleic acid amplification reaction" in Claim 1, because "the method does not recite method steps of isothermal amplification and therefore it is unclear how the recitation limits the

method". Claim 1 has been amended to place the recitation in the preamble of the claim rather then as a limitation following the transition.

B. Claims 1-22 were rejected as indefinite for the recitation "a diagnostic nucleotide for the single nucleotide polymorphism about one to four nucleotides from a 3' terminal nucleotide of the detector primer" in Claim1, because it was unclear whether the 3' terminal nucleotide is a diagnostic nucleotide. Claim 1 has been amended as recommended in Paper No. 3 to address this issue.

C. Claims 1-22 were rejected as indefinite for the recitation "determining efficiency" in step (c) of claim 1, because "efficiency" can be either a quantitative or qualitative term both of which require definition or criteria for determining. Claim 1 has been amended as recommended in Paper No. 3 to define efficiency.

D. Claims 2 and 3 were rejected as indefinite for the recitation "single nucleotide polymorphism is identified" because "identified" lacks proper antecedent basis in Claim 1. Claim 2 has been canceled, and Claim 1 has been amended to provide antecedent basis.

E. Claim 4 was rejected as indefinite for the recitation " two detector primers are used to identify which of two possible alleles is present in the target sequence", because "identify" and "alleles" lack proper antecedent basis in Claim 1. Claim 1 has been amended to provide antecedent basis for "identify", and Claim 4 has been amended as recommended in Paper No. 3 to address the indefiniteness of "alleles".

F. Claim 5 was rejected as indefinite for the recitation "identify the nucleotide present in the target sequence at a position of the single nucleotide polymorphism", because both "identify" and "the position" lack proper antecedent basis in Claim 1. Claim 1 has been amended to provide antecedent basis for "identify", and "the position" has been deleted from Claim 5.

G. Claim 13 was rejected as indefinite for the recitation "SDA, 3SR, NASBA and TMA", because these are abbreviations. As recommended in Paper No. 3, the words represented by these acronyms have been added to Claim 13.

H. Claim 17 was rejected as indefinite for the recitation "detected by means of a label associated with the detector primer", because "associated" is a non-specific relational term. The phrase "associated with" has been deleted from Claim 17 and replaced by "attached to".

I. Claim 19 was rejected as indefinite for the recitation "fluorescence is detected as an indication of the presence of the single nucleotide polymorphism", because "indication" is a non-specific relational term. The phrase "an indication of" has been deleted from Claim 19, and the word "identifying" has been added.

J. Claim 20 was rejected as indefinite for the recitation "fluorescence polarization is detected as an indication of the presence of the single nucleotide polymorphism", because "indication" is a non-specific relational term. The phrase "an indication of" has been deleted from Claim 20, and the word "identifying" has been added.

K. Claim 22 was rejected as indefinite for the recitation of "prior to amplifying, displacing the hybridized detector primer", because it is unclear how this phrase fits into the method of Claim 1. Claim 22 has been amended to clarify the claimed method.

II. Obviousness

A. Claims 1-5, 7-12, 14-18 and 21 were rejected under 35 U.S.C. §103 (a) as being obvious over Newton et al. (U.S. Patent No. 5,595,890) in view of Reynolds et al. (U.S. Patent No. 5,763,184) and Krausa et al. (Human Immunology, 1995, 44: 35-42). It was asserted that Newton discloses all elements of the method of Claim 1 except that Newton does "not teach the diagnostic nucleotide is about one to four nucleotides from a 3' terminal nucleotide". It was then asserted that "diagnostic nucleotides adjacent to the 3' terminal nucleotide were well known in the art at the time the invention was made as taught by Reynolds et al. and Krausa et al.". Thus, it was asserted that it "would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Reynolds et al. ...to the diagnostic primers of Newton et al".

Applicants respectfully traverse. Someone of ordinary skill in the art at the time of the claimed invention would have noted, as the Examiner has, that Newton only teaches the use of the 3' terminal nucleotide as the diagnostic nucleotide. Also, Newton teaches those skilled in the art that the reason for utilizing the 3' terminal nucleotide as the diagnostic nucleotide is for purposes of differentiating those samples containing the target single nucleotide polymorphism ("SNP") from those samples that do not contain the target SNP, because

> where there is a mismatch between ... the 3' terminal end of the diagnostic primer and the corresponding nucleoside triphosphate in the sample nucleic acid no primer extension will be effected. Where, however, the 3' terminal nucleoside triphosphate is complementary with the corresponding nucleoside triphosphate in the sample nucleic acid, primer extensions will be effected.

(Column 7, line 64 – Column 8, line 3).

This differentiation process, based on the complementarity or non-complementarity of the 3' terminal nucleotide of Newton's diagnostic primer to the target nucleotide of the SNP is further emphasized at:

1. Column 21, lines 14 – 23.

" Contacting the nucleic acid strand under the hybridizing conditions, with a diagnostic probe having a 3'-terminal nucleotide complementary to the normal nucleotide (-N) in the presence of appropriate nucleoside triphosphates and an agent for polymerization of the nucleoside triphosphates results in chain extension of the diagnostic primer in the 3'-direction as show in FIG.1(b). No such chain extension arises where a diagnostic primer is used in which the 3'-terminal nucleotide is complementary to the suspected variant nucleotide (-M).

2. Column 22, lines 20 – 28.

"Since in the Figure the 3'-terminal nucleotide is normal as is the relevant nucleotide in the test sample, amplification will take place. Similarly amplification will take place if the relevant nucleotide in the test sample is a variant nucleotide and the diagnostic primers used also carry a 3'-terminal variant nucleotide. No such amplification will however arise where a mismatch arises between the relevant nucleotide in the sample and the 3'-terminal nucleotide of the diagnostic primer.

Furthermore, one of ordinary skill in the art reading Reynolds with the background of the earlier Newton disclosure would not be motivated to use the hypothesized primers with sequences that "hybridize to the target sequence such that the polymorphic site hybridizes at or near the 3' end of the primer," because Reynolds teaching regarding such differentiating methods is consistent with Newton. Specifically, in its teaching regarding an amplification reaction to differentiate nucleic acid sample with the target SNP from that without the target SNP, Reynolds notes the necessity of being able "to carry out the primer extension necessary for an amplification reaction" (Column 8, lines 48 – 49). Thus, Reynold's teaching as it applies to an amplification method using a diagnostic primer is consistent with Newton.

The actual working Examples of Reynolds do not utilize an amplification method with a diagnostic primer, and hence do not offer any practical teaching relating to such a method to one of ordinary skill in the art. The working Examples of Reynolds present methods wherein primers that flank a target sequence of interest, are used to amplify the target sequence, and then probes are hybridized to the amplified sequence to identify whether certain alleles are present. As noted by Reynolds, such a probe hybridization method is different from an amplification method (see Column 8, lines 45 – 49).

Thus, it is respectfully submitted that one of ordinary skill in the art would not be motivated to combine the teachings of Newton and Reynolds to achieve the claimed invention. The disclosure of Reynolds that relates to an amplification method is hypothetical, because it was not actually practiced by Reynolds as evidenced by the working Examples. Also, the teaching of Reynolds regarding the necessary characteristic for detection/identification of a SNP in an amplification reaction (ability to carry out

primer extension) is consistent with Newton, and Newton teaches that the terminal nucleotide of the primer being the diagnostic nucleotide is necessary for such primer extension based differentiation.

It is respectfully submitted that the teachings of Krausa et al. do not provide any teaching that, combined with that of Newton et al., would render the claimed invention obvious.

B. Claim 6 was rejected under 35 U.S.C. §103 (a) as being obvious over Newton et al. in view of Reynolds et al. and Krausa et al. as applied to Claim 1 and further in view of Mullis et al. (U. S. Patent No. 4,683,195).

It is respectfully submitted that the remarks above relating to the obviousness rejection of Claim 1 are equally applicable to this rejection.

C. Claim 13 was rejected under 35 U.S.C. §103 (a) as being obvious over Newton et al. in view of Reynolds et al. and Krausa et al. as applied to Claim 1 and further in view of Guatelli et al. (Prod. Natl. Acad. Sci. USA, 1990, 87:1874-1878).

It is respectfully submitted that the remarks above relating to the obviousness rejection of Claim 1 are equally applicable to this rejection.

D. Claims 19 and 20 were rejected under 35 U.S.C. §103 (a) as being obvious over Newton et al. in view of Reynolds et al. and Krausa et al. as applied to Claim 1 above and further in view of Chen et al. (Nucleic Acids Research, 1997, 25(2):347-353).

It is respectfully submitted that the remarks above relating to the obviousness rejection of Claim 1 are equally applicable to this rejection.

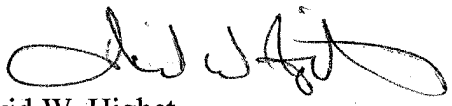
E. Claim 22 was rejected under 35 U.S.C. §103 (a) as being obvious over Newton et al. in view of Reynolds et al. and Krausa et al. as applied to Claim 1 and further in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696).

It is respectfully submitted that the remarks above relating to the obviousness rejection of Claim 1 are equally applicable to this rejection.

III. Conclusion

The claims of the present application are believed to in condition for allowance, and early notice thereof is respectfully requested. Attached hereto is a marked-up version of the changes make to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,



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